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THE METABOLIC AND THERMOREGULATORY RESPONSES OF RHESUS MONKEYS TO COMBINED EXERCISE AND ENVIRONMENTAL HEAT LOAD

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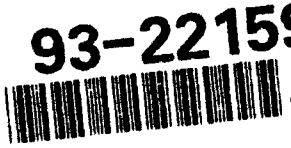

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The Office of Public Affairs has reviewed this paper, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This paper has been reviewed and is approved for publication.

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12. ABSTRACT *(Maximum 200 words)*

The purpose of the present research was to characterize the effects of selected physiological stressors such as work and various environmental heat loads in rhesus monkeys. Nonhuman primates (N=6) were behaviorally conditioned to exercise in a wheel ergometer at ≈ 3 METs. On separate days, each monkey attempted six work/rest cycles (10 min work:1 min rest) at 15, 25 and 35 °C dry bulb temperature, vapor pressure < 10 mmHg. Core temperature (T_{co}), body weight (BW) and blood samples were taken immediately before and after exercise. Excessively high heat storage rates dictated that the 35 °C trial be limited to three work/rest bouts. Sweat rate (as determined by the change in BW over time) and the change in T_{co} during exercise were significantly greater during the 35 °C trial as compared to the 15 and 25 °C trials. Glucose levels (mean ± SE) declined significantly during exercise from 4.35 ± 0.1 and 4.58 ± 0.4 mM to surprisingly low levels of 1.67 ± 0.2 and 1.76 ± 0.2 mM in the 15 and 25 °C trials, respectively. Increases in blood lactate, glycerol and triglycerides were observed independent of environmental temperature. Free fatty acids increased during exercise in the 15 and 25 °C trials but declined slightly during the shorter 35 °C trial. The findings of this study indicate that the increased heat storage observed at higher environmental heat loads appears to substantially limit the amount of work these primates can perform, possibly the result of a limited sweat production capacity. Additionally, plasma glucose following exercise decreased to levels not typically seen in humans. The general metabolic profile in these primates was otherwise similar to that observed in humans at this work level.

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THE METABOLIC AND THERMOREGULATORY RESPONSES OF RHESUS MONKEYS TO COMBINED EXERCISE AND ENVIRONMENTAL HEAT LOAD

INTRODUCTION

Several investigations have examined the thermoregulatory responses of rhesus monkeys (*Macaca mulatta*) to heat exposure. Resting and exercise studies have primarily concentrated on mechanisms of thermal balance (13, 18, 19, 28), metabolic rate (19), and manipulation of central mechanisms of thermoregulation (1, 14, 25). These studies have demonstrated many similarities between the thermoregulatory systems of rhesus and human subjects. Therefore, the rhesus monkey is considered an appropriate model for conducting selected thermoregulatory experiments, as research in the area of physiological stress cannot always be performed with humans for safety and ethical reasons.

To identify the further use of the rhesus monkey as a research model for the associated fatigue factors during exercise and heat stress, we have integrated exercise into a multidimensional primate model (3). The incorporation of exercise into research using nonhuman primates has been used previously (9, 10, 12, 17, 21, 24, 30, 33, 34, 35, 36, 40). Our study characterizes the metabolic and thermoregulatory responses of rhesus monkeys to two common occupational stressors, i.e., work and a varied environmental heat load, and compares the responses of the rhesus to that of humans. The study furthers the validity of using the rhesus monkey as a model for metabolic and environmental stress research.

METHODS

Primates. Six female rhesus monkeys, weighing 4.4-5.5 kg, served as subjects. These monkeys were housed in individual cages in a room maintained at an ambient temperature (T_a) of 22 ± 2 °C, 50% relative humidity and a 12:12 h light:dark cycle. The typical diet of the primates consisted of Purina Monkey Chow supplemented with fruit.

Water was available ad libitum. Prior to each experimental session, monkeys were fasted for 18-20 h (water available).

Experimental procedures. All testing was performed in an environmental chamber maintained at 15, 25 or 35 °C, depending on the experimental trial, each with a vapor pressure < 10 mmHg. Associated technical problems made it necessary to repeat selected experiments (data not reported); thus, a completely randomized design was not possible. The monkey was first transferred to the chamber for 60 min prior to exercise to allow for the stabilization of any acute physiological adjustments to the environment. During this time, the primate was placed in a restraining chair. Approximately, 10 min prior to being transferred to the exercise wheel, the pre-exercise blood sample was obtained for subsequent determination of blood lactate, plasma glucose, plasma triglycerides (TG), plasma glycerol, plasma free fatty acids (FFA), hemoglobin (Hb) and hematocrit (Hct). Body weight (BW) [Weightmeter 533, Electroscale Co., Santa Rosa, CA] and core temperature (T_{CO}) measurements [model 701 rectal probe, Yellow Springs Instruments, Yellow Springs, OH] were also obtained immediately prior to exercise.

Immediately following the pre-exercise T_{CO} measurement, the monkey was placed in the ergometer and the exercise protocol was begun. Previously, the animals were behaviorally conditioned to run in a primate exercise wheel, as described by Sherry and Constable (32) and were able to complete six work/rest cycles (10 min work:1 min rest) at a minimum of 3 mph at room temperature. In the present study, the animals maintained an average speed of 3.2 to 3.4 mph at the three environmental temperatures. During the experimental trials, the primates successfully completed the six work/rest cycles in the 15 and 25 °C trials. However, the 35 °C experimental trial was limited to three work/rest bouts as preliminary testing showed that excessively high heat storage rates occur in the rhesus at this temperature concurrent with exercise. This rate of heat storage might have induced

irreversible heat injury if these primates attempted the full six exercise bouts. In these pilot experiments, T_{CO} was monitored using radio telemetry (3).

During exercise, respiratory measures (VO_2, VCO_2, RER) were determined by drawing room air [Kurz 565-7A Mass Flowmeter, Monterey, CA] at a constant rate (40-45 L/min) through a Plexiglas canopy enclosing the exercise wheel. Aliquots of expired air were sampled for oxygen (O_2) and carbon dioxide (CO_2) content [Perkin Elmer Medical 1100 Gas Analyzer, Pomona, CA] from a mixing chamber connected to the canopy. These aliquots were assumed to be representative samples; the motion of the wheel mixes the air within the canopy while the air flow creates a modest negative pressure inside the canopy. The validity of this sampling procedure was indirectly confirmed by conducting a series of alcohol burns. Because the volume of the wheel canopy is ≈1,400 L and air is pulled through at only 40-45 L/min, the time required to completely flush the canopy is ≈ 30 min. For this reason, we did not measure respiratory variables during the 35 °C trial because the total exercise time was only 30 min. The values reported for the 15 and 25 °C trials are averages for the final 10-min work cycle of each trial. The outputs of the O_2 and CO_2 analyzers and the flowmeter were interfaced with a Macintosh IIx computer. Analog-to-digital conversions were handled by a program (4) written in LabVIEW graphical programming language, Version 2.0.6 (National Instruments, Austin, TX).

After the final work cycle ended, the monkey was promptly removed from the wheel and returned to the restraint chair. Both the post blood sample and T_{CO} measurement were obtained within 3 min after exercise was terminated. This time period was necessary to transfer the monkey from the wheel to the chair. Post-exercise BW was then measured.

Changes in body water. During the exercise period, all body waste was captured in a pan located beneath the wheel; the pan contained mineral oil used to minimize evaporation of the waste. The pan was weighed both before and after exercise. Thus, the weight of the

urine and excrement was subtracted from the total body weight loss to calculate body water loss. Body water lost as respiration was not measured but was assumed to be minimal. Sweat rate was determined using the following equation:

$$\text{Sweat rate} = \frac{[(BWpre - BWpost) - (PANpost - PANpre)] \times 1000}{\text{exercise duration (min)}} = \text{g/min}$$

where: BWpre = body weight before exercise, BWpost = body weight after exercise, PANpre = pan weight before exercise and PANpost = pan weight after exercise. All weights were expressed in kilograms.

Blood collection and analysis. Venous blood was obtained (5-6 ml) with a 20-gauge hypodermic needle from the saphenous vein of a leg both before exercise and at 3 min following exercise. The blood sample was transferred from the syringe to a test tube containing 0.07 ml of 15% liquid EDTA. A 500 µl aliquot of this blood was then deproteinized in 1 ml cold 8% perchloric acid, centrifuged and the supernatant stored at -70 °C until analysis for blood lactate concentration (16). Measurements of Hb and Hct were also obtained to be used in the determination of percent changes in blood, plasma and red cell volume by the method of Dill and Costill (5). The Hb was measured in duplicate by the cyanmethemoglobin technique. The Hct was measured in triplicate by the microhematocrit centrifuge technique. The remaining blood was centrifuged and the plasma separated for subsequent analysis of glucose (Sigma Kit, No. 510), FFA (7, 22, 27), and total TG and free glycerol (Sigma Kit, No. 337-B).

Blood volume calculations. Percent changes in blood, cell and plasma volumes were calculated from Hb and Hct values using the equations of Dill and Costill (5):

$$BV_A = BV_B (Hb_B / Hb_A)$$

$$CV_A = BV_A\,(Hct_A)$$

$$PV_A = BV_A - CV_A$$

$$\Delta BV, \% = 100\,(BV_A - BV_B) / BV_B$$

$$\Delta CV, \% = 100\,(CV_A - CV_B) / CV_B$$

$$\Delta PV, \% = 100\,(PV_A - PV_B) / PV_B$$

where: BV is blood volume, CV is cell volume and PV is plasma volume. The subscripts B and A refer to before and after exercise, respectively.

Statistical analysis. Comparisons of the three experimental trials (15, 25, 35 °C) were made using a three-way analysis of variance (ANOVA; monkey x temperature x time) with repeated measures when both a pre and post measurement existed. The level of significance was set at $P \leq 0.05$ and significant differences in change over time (deltas) between trials were identified using post-hoc Duncan's Multiple Range Tests. Significant differences in pre to post values were found using individual t-tests. The respiratory variables (VO_2, VCO_2, RER), blood volume changes, body weight loss and sweat rate were analyzed using a two-way ANOVA (monkey x temperature) and Duncan's Multiple Range Tests.

RESULTS

Core temperature. As seen in Figure 1, the T_{CO} response during the 15 and 25 °C trials did not change greatly from pre to post. Surprisingly, T_{CO} during the 15 °C trial tended to decrease slightly during exercise. A three-way ANOVA performed on T_{CO} indicated a significant interaction (time x temperature) effect. Post-hoc analysis revealed a significantly greater change in T_{CO} during the 35 °C trial than in the 15 and 25 °C trials. This large increase in body heat storage occurred at 35 °C despite the shortened exercise time.

Sweat rate. The estimated sweat rates are displayed in Figure 2. A two-way ANOVA performed on sweat rate (grams of sweat/min) during exercise indicated a significant temperature effect. Post-hoc analysis revealed that sweat rate at all temperatures differed significantly from one another (35 > 25 > 15 °C; P = 0.0001).

Plasma glucose and blood lactate. A three-way ANOVA performed on pre and post glucose levels showed a significant interaction effect (time x temperature; Figure 3). Post-hoc analysis indicated a significant difference between the overall decrease in glucose at 35 °C vs the 15 and 25 °C trials. This difference was likely the result of a shortened exercise period in the 35 °C trial and would probably have not persisted had the monkeys exercised for 60 min. More importantly, all temperatures showed a significant decrease in glucose over time. The blood lactic acid was less affected by this level of exercise (Figure 4). Lactic acid accumulation tended to modestly increase during work across all trials. However, the three-way ANOVA found no significant differences in the lactate response.

Plasma FFA, glycerol and TG. As shown in Figure 5, plasma FFA in both 15 and 25 °C trials increased from pre to post, whereas the 35 °C FFA value tended to decrease slightly. Further analyses performed on these measures indicated a significant interaction (time x temperature) effect. Post-hoc analysis suggested a significantly greater change over time in the 15 and 25 °C trials than in the 35 °C trial. A three-way ANOVA performed on glycerol values revealed a significant temperature effect (Figure 6). Post-hoc analysis showed that during the 25 °C trial, the mean value across time was significantly greater than that observed at 15 and 35 °C. This finding may have resulted from the significantly elevated pre-exercise glycerol value of the 25 °C trial as the slope of the lines from pre to post were similar at all three temperatures. Therefore, glycerol increased significantly during work at all temperatures while a two-way ANOVA revealed no significant

differences between the change in glycerol over time. Not surprisingly, plasma TG responses (Figure 7) were generally similar to those of glycerol. A three-way ANOVA indicated a significant temperature effect on TG. Post-hoc analysis revealed a greater overall TG value at 25 vs 35 °C. As with glycerol, the elevated pre TG value of the 25 °C trial may have resulted in this significant finding because again the slope of the lines from pre to post were not significantly different, indicating similar change.

Hb and Hct. Three-way ANOVAs were performed on Hb and Hct. Values for the variables are shown in Table 1. No significant differences were found among Hb values. The overall Hct values were significantly greater during 25 °C than during 15 and 35 °C, revealed by post-hoc tests.

Blood volume and respiratory measures. Two-way ANOVAs performed on the changes in BV, PV and CV indicated no significant changes in these values over time (Fig. 8). The respiratory measures across two trials are given in Table 2. Two-way ANOVAs indicated no significant differences between 15 and 25 °C for VO_2, VCO_2 and RER, respectively.

DISCUSSION

To further characterize the rhesus monkey as a research model for the associated fatigue factors during exercise and heat stress, we designed this study to establish baseline data on the physiological and metabolic responses of this primate to exercise at three environmental temperatures. These measures would allow some comparison of the responses of the rhesus to that of humans to determine the potential validity of the use of the rhesus as a model for metabolic and environmental stress research. Many of these responses have not been previously reported in exercising, nonhuman primates. The range of environmental temperatures used here was somewhat modest (i.e., 15, 25, 35 °C), all

with low water vapor pressures. Blood metabolites and volumes, core temperature, VO_2 and sweat loss were examined during each trial. Maximal VO_2 has never been measured on a rhesus monkey; it would require extensive animal training to obtain such a measurement on an exercising monkey. However, based on previous data in another primate species (24) and human maximal values, we have estimated that the exercise intensity used in this study was approximately 30 - 40% of the monkeys' VO_2 max.

Core temperature. As has been demonstrated previously (13, 18), the maximal sweat rate capacity of the rhesus monkey is less than that of humans; thus their ability to thermoregulate under stressful environmental conditions is not as effective. This predisposition was demonstrated in the 35 °C trial where the monkeys stored heat at a prohibitively high rate during 30 min of exercise (Fig. 1). These trials were terminated following the third work/rest bout for the safety of the monkeys. However, during both the 15 and 25 °C trials, the monkeys apparently stabilized their core temperature well throughout exercise, and thus appear to thermoregulate effectively while working at these ambient temperatures. It is worth noting that the starting core temperatures were perhaps 0.5-1.0 °C higher than might be expected at all three environmental temperatures (18). These higher starting core temperatures may reflect a stress-related response to the handling these monkeys received while they were transferred to and from the restraint chair.

Sweat rate. Not surprisingly, sweat rate was greatest in the 35 °C trial; this temperature created the greatest heat stress for the animal. However, the high heat storage rate reflected by the increased core temperature indicated that sweat production was insufficient for thermal balance during the 35 °C trial. The maximum sweat rate in rhesus monkeys has previously been shown to be 0.07 $mg/cm^2/min$ (18) whereas human sweat rate can attain values of approximately 1 $mg/cm^2/min$ (13, 15). This limited sweat rate in the rhesus appears to reduce its thermoregulatory capacity during exercise under hot, dry

conditions. We have previously observed that the thermoregulatory compensation for these monkeys even during rest is insufficient at ambient temperatures of 40 °C at high relative humidities (8).

Plasma glucose. Following the 1-h runs in our study, the plasma glucose levels observed in these monkeys were much lower than levels normally attained in exercising humans (Figure 3). These glucose levels may reflect low liver glycogen stores as a result of fasting. This response was also surprising as we have run several of these monkeys to exhaustion at room temperature on at least ten different times and have found that they can exercise at the same intensity used in our present study for 2.5 - 3 h. The fact that the monkeys used for these exhausting runs were not fasted may have influenced their exercise capacity. Unfortunately, we did not obtain blood samples at the time of the exhausting runs; therefore, substrate profiles on these animals were not available. It would be interesting in the future, however, to measure these primates' metabolic response to extended exercise. Moreover, in a separate experiment, following a 30-min training run at an ambient temperature of 23 °C, one of these monkeys incurred a hypoglycemic reaction. The monkey was treated and recovered fully. Plasma analysis revealed a glucose level of 1.22 mM. Again, this monkey was fasted prior to exercise and thus, nutritional status may have contributed to this response.

Blood lactate. True blood lactate levels are difficult to obtain; these monkeys often struggle somewhat when they are removed from the transport cage or primate exercise wheel and placed into the restraint chair for blood sampling. This exertion can easily elevate lactate levels even prior to exercise (e.g., 3-5 mM). Surprisingly, these remarkably high values can occur following only a brief (30-60 sec) struggle. Trials were repeated when suspect lactate values were observed. Still, our reported lactic acid levels may be somewhat elevated due to this behavior: probably more so for the pre-exercise

observations as the monkeys were more likely to struggle prior to exercise. Only very modest elevations in blood lactate would be expected at exercise intensities below 40-50% VO_2 max (2) without any additional heat stress. Lactic acid response in previous human studies has shown that an increase in blood lactate accumulation does appear following submaximal exercise in the heat at higher intensity work bouts than those used in our study (6, 23, 38). However, whether this is the result of an increase in lactate production from the active musculature or a decline in lactate removal by the liver, heart and inactive skeletal muscle is controversial (39). A decrease in hepatic blood flow does occur during exercise in the heat (31) as an increase in cutaneous blood flow is necessary for heat dissipation, supporting a decline in uptake by hepatic tissue. The concept of a decrease in lactate removal is also supported by Nielsen et al. (26) who found no significant difference in lactate release from the exercising musculature in cool (18-20 °C) or hot (40 °C) conditions.

Plasma FFA. During exercise at 40% VO_2 max, Walker et al. (37) showed an initial decline in FFA from basal levels followed by steadily increasing FFA levels. The FFA levels had not returned to baseline until 20 min into the exercise period. Knapik et al. (20) demonstrated similar results with a return to baseline FFA values after 30 min of exercise. This initial decline in FFA may reflect a delay in FFA mobilization. Our findings demonstrate this pattern, as following 30 min of exercise in the 35 °C trial, the FFA level was below the pre-exercise value. However, during the 15 and 25 °C trials, circulating FFA levels were elevated following the 60 min exercise bouts. Thus, the initial decline in FFA levels may have occurred in all 3 trials in our study but was only observed in the shortened exercise bout. Randle et al. (29) have investigated a carbohydrate-sparing effect of fatty acids termed the glucose-fatty acid cycle. This concept would suggest that the depleted plasma glucose levels in the 15 and 25 °C trials may have acted as a stimulus to increase the rate of mobilization of the FFA from adipose tissue. This increased

mobilization would not have occurred at 35 °C because plasma glucose did not decrease as much during this shortened trial. Finally, ambient temperature has been previously shown to have no effect on FFA response to exercise; Fink et al. (11) showed an increase in FFA during exercise in both hot and cold conditions (41 and 9 °C, respectively), with no difference between the two experimental conditions.

Plasma glycerol and TG. Glycerol and total TG increased over time in all three trials as is typically observed in humans during exercise (Figures 6 & 7). The overall glycerol and TG level during the 25 °C trial was significantly elevated above those for the 15 and 35 °C trials; however, the pre to post change (delta) in all three trials was similar. Therefore, it appears that ambient temperature did not play a role in the responses of glycerol and TG to exercise.

Blood volume changes. At the onset of exercise, there is typically a large reduction in BV as plasma water shifts into the active musculature. After this initial hemoconcentration, BV remains relatively constant throughout the remainder of the exercise period. During recovery immediately following exercise, plasma water tends to return to the vascular space. Surprisingly, after the exercise bout in our study, BV (calculated using Hb values) was slightly elevated in all three trials (NS). Some return of plasma water to the vascular space may have occurred as the post-exercise blood sample was obtained ≈ 3 min after exercise ended; however, this possibility still does not explain the elevated BV post-exercise compared to the pre-exercise volume.

Respiratory measures. As shown in Table 2, VO_2, VCO_2 and RER were not significantly different between the 15 and 25 °C trials. As explained earlier, these variables could not be accurately measured during the shortened 35 °C trial. A review of the literature by Young (38) has demonstrated little or no difference in VO_2 and RER during exercise in the heat and in the cold as opposed to a more temperate environment. However,

Dimri et al. (5) have suggested an increase in anaerobic metabolism during exercise in the heat which would not be reflected in oxygen consumption.

In conclusion, the major finding of this investigation was the high rate of body heat storage in the 35 °C trial. However, this finding was also somewhat constraining because this level of heat storage dictated that this trial be limited to only three work/rest cycles, whereas in the 15 and 25 °C trials, the monkeys completed six work/rest cycles. Consequently, full comparisons of the post exercise values became somewhat difficult because the duration of the exercise bouts differed. One might expect greater changes in metabolic responses during the 35 °C trial because the large increase in core temperature over the shorter time would seem more stressful to the animal. However, the shortened duration of the 35 °C trial may have curtailed any differences in the response to ambient temperature. Overall, this study demonstrates that the rhesus monkey exhibits a physiological response to exercise stress similar to that seen in humans. However, exercise combined with increased heat stress is not easily tolerated by this primate. Further investigation of carbohydrate metabolism in this species is warranted.

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Table 1. Hematological values before and after submaximal exercise at three environmental temperatures.

	PRE	POST
HEMOGLOBIN (mg/dl)		
15 °C	14.61 ± 0.3	14.51 ± 0.4
25 °C	13.64 ± 0.3	13.38 ± 0.2
35 °C	13.96 ± 0.3	13.66 ± 0.3
HEMATOCRIT (%)		
15 °C	39.77 ± 0.9	39.13 ± 0.5
25 °C	43.23 ± 1.0	40.72 ± 1.5*†
35 °C	39.42 ± 1.0	38.31 ± 0.4

Values are means ± SE; $P \leq 0.05$; *Significantly different from respective pre value.

†Signif. elevated mean value across time vs. other trials.

Table 2. Oxygen consumption, carbon dioxide production and respiratory exchange ratio during exercise at two environmental temperatures.

Temperature	VO_2	VCO_2	RER
15 °C	135.9 ± 5	120.4 ± 5	0.89 ± 0.01
25 °C	140.5 ± 6	125.6 ± 6	0.89 ± 0.01

Values are means ± SE; $P \leq 0.05$. Values for 35 °C were not obtained; see text.

No significant differences between values.

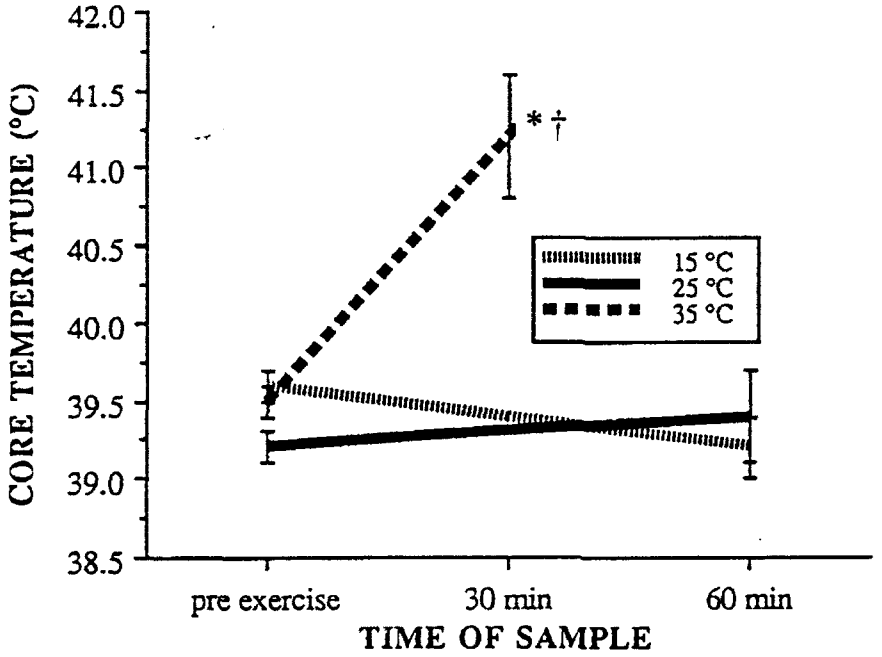

Figure 1. Core temperature response before and after exercise at three environmental temperatures. Values are means ± SE; $P \leq 0.05$. *Significantly greater than the pre value. †Significantly greater than the other trials over time.

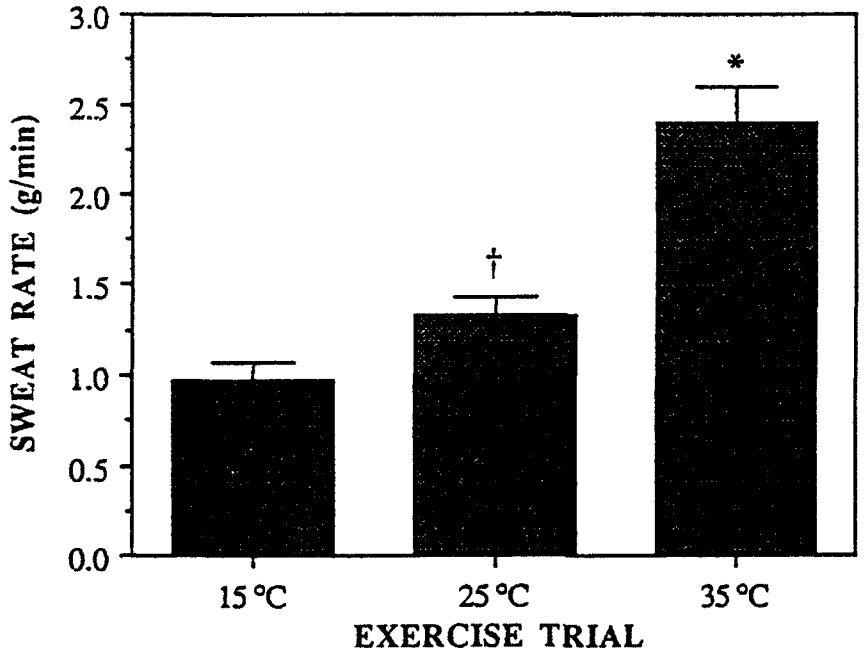

Figure 2. Calculated sweat rate during exercise at three environmental temperatures. Values are means ± SE; $P \leq 0.05$. *Significantly greater than 15 and 25 °C. †Significantly greater than 15 °C.

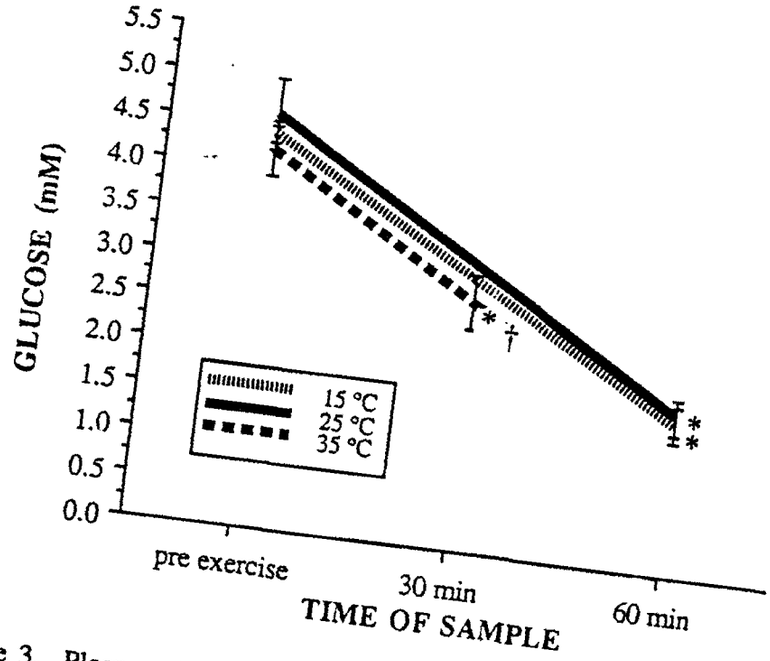

Figure 3. Plasma glucose response before and after exercise at three environmental temperatures. Values are means ± SE; $P \leq 0.05$. *Significantly different from the pre value. †Significantly less change than the other trials.

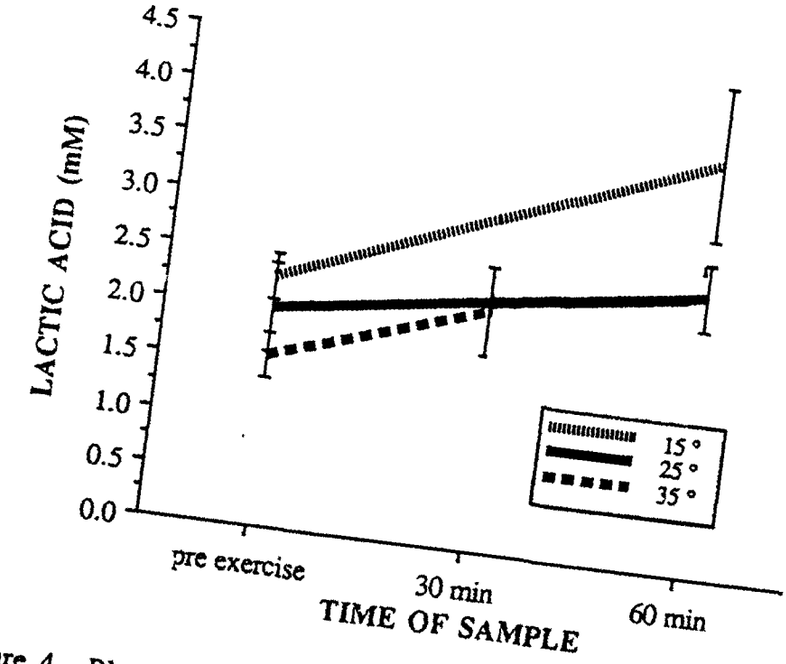

Figure 4. Blood lactate response before and after exercise at three environmental temperatures. Values are means ± SE; $P \leq 0.05$. No significant differences.

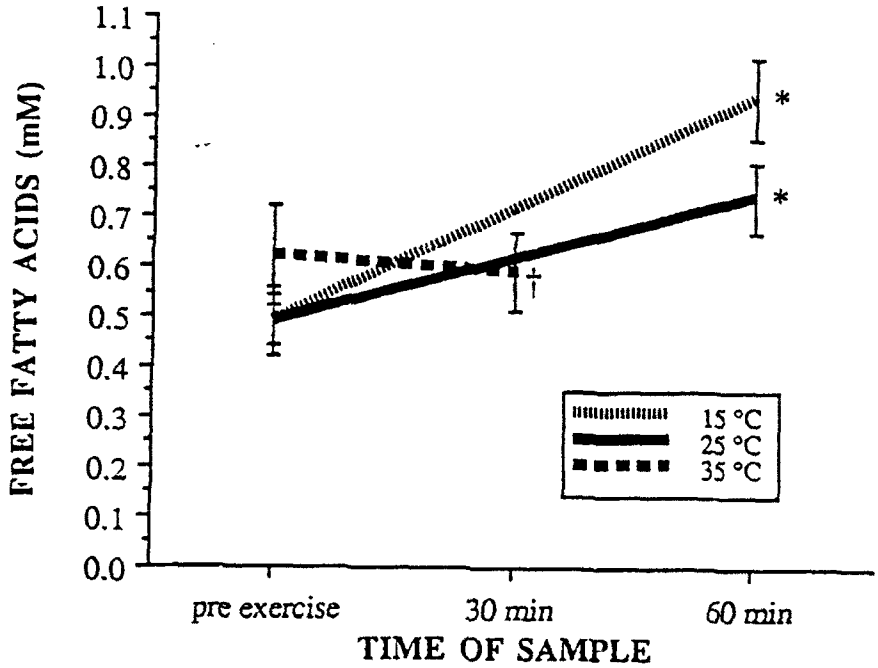

Figure 5. Plasma free fatty acid response before and after exercise at three environmental temperatures. Values are means ± SE; $P \leq 0.05$. *Significantly different from pre value. †Significantly less change from other trials.

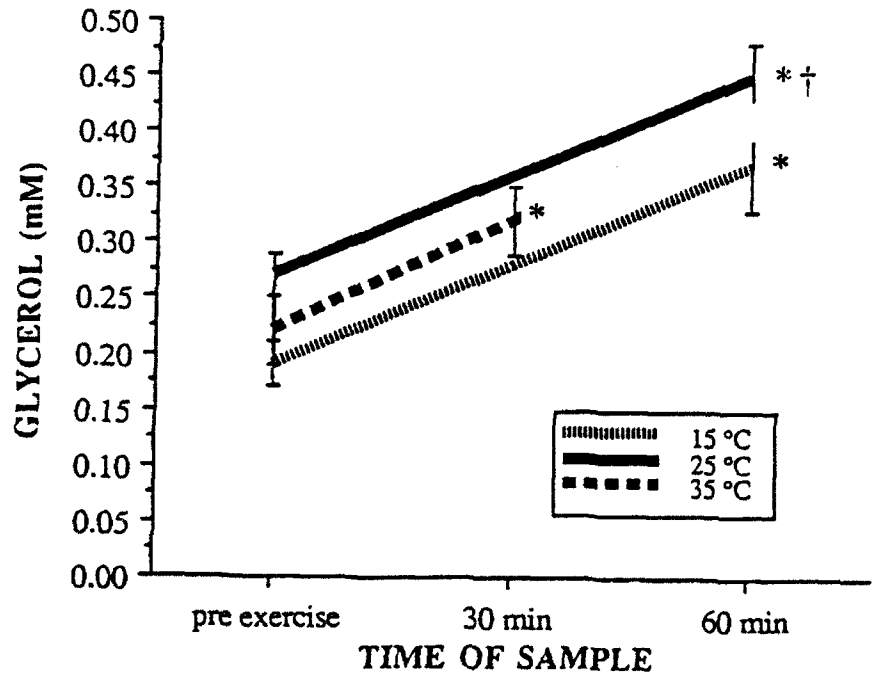

Figure 6. Plasma glycerol response before and after exercise at three environmental temperatures. Values are means ± SE; $P \leq 0.05$. *Significantly greater than pre values. †Significantly elevated levels than other trials overall.

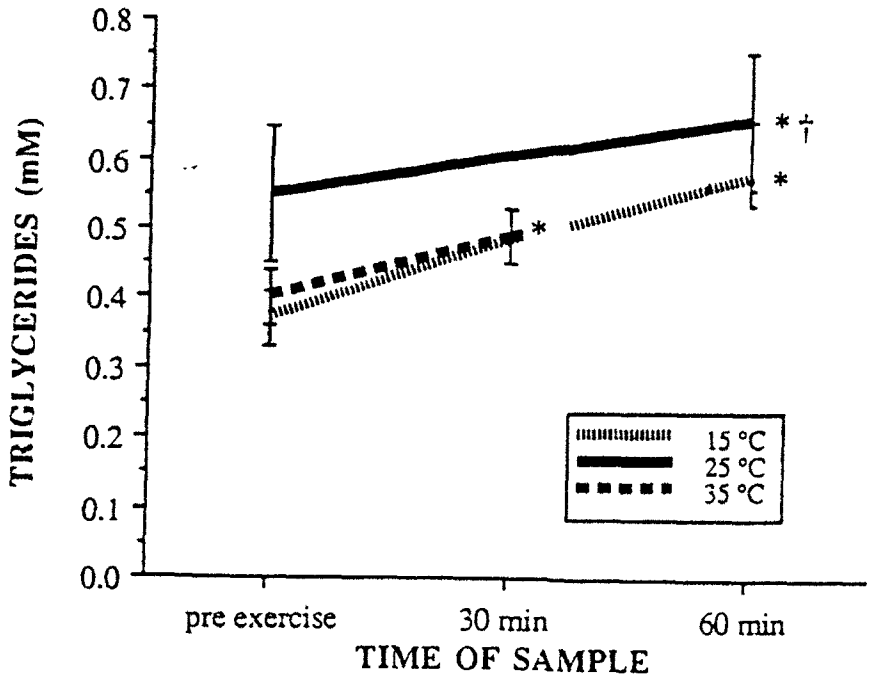

Figure 7. Plasma total triglycerides response before and after exercise at three environmental temperatures. Values are means ± SE; $P \leq 0.05$. *Significantly greater than pre values. †Significantly elevated level than other trials overall.

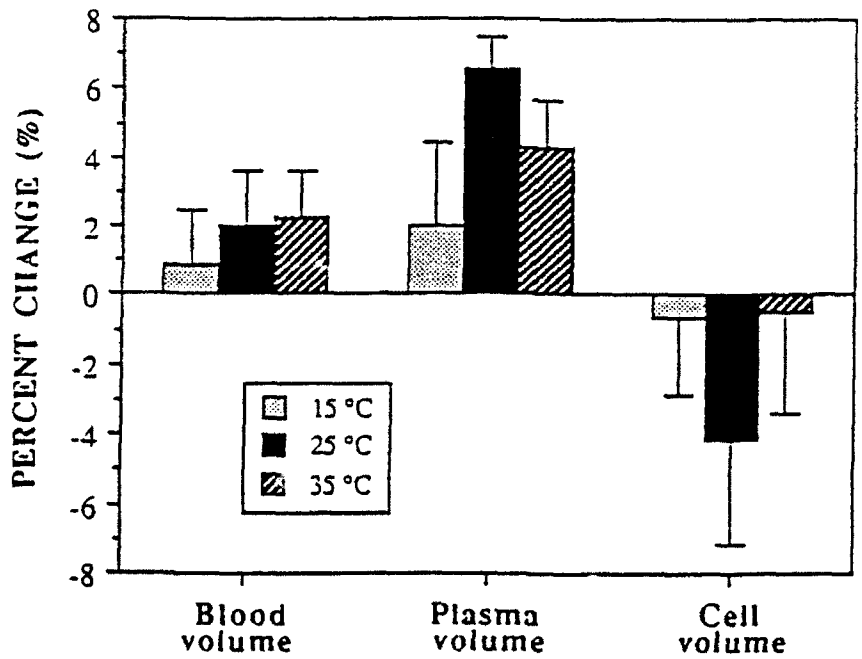

Figure 8. Changes in blood volume, plasma volume and red cell volume during exercise at three environmental temperatures. Values are means ± SE; $P \leq 0.05$. No significant differences.